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ABSTRACT

This article presents the World Health Organization's (WHO) recommendations on the use of dengue vaccine excerpted from the WHO position paper on dengue vaccine – September 2018, published in the Weekly Epidemiological Record [1]. This position paper replaces the July 2016 WHO position paper concerning the first licensed dengue vaccine, CYD-TDV [2]. The position paper presents new evidence that became available in November 2017. A retrospective analysis of data from clinical trials, using a new serological assay classified trial participants according to their dengue serostatus prior to receipt of the first vaccine dose. The analysis revealed an excess risk of severe dengue in seronegative vaccine recipients compared to seronegative non-vaccinated individuals, while confirming long-term protection in seropositive individuals [3]. The paper provides revised guidance on dengue vaccination strategies from a population health perspective.

Footnotes to this paper provide a number of core references including references to grading tables that assess the quality of the scientific evidence, and to the evidence-to-recommendation table. In accordance with its mandate to provide guidance to Member States on health policy matters, WHO issues a series of regularly updated position papers on vaccines and combinations of vaccines against diseases that have an international public health impact. These papers are concerned primarily with the use of vaccines in large-scale immunization programmes; they summarize essential background information on diseases and vaccines, and conclude with WHO's current position on the use of vaccines in the global context. Recommendations on the use of dengue vaccine CYD-TDV were discussed by SAGE in April 2018; evidence presented at the meeting can be accessed at: http://www.who.int/immunization/sage/meetings/2018/april/presentations_background_docs/en/

The live attenuated dengue vaccine CYD-TDV has been shown in clinical trials to be efficacious and safe in persons who have had a dengue virus infection in the past (seropositive individuals), but carries an increased risk of severe dengue in those who experience their first natural dengue infection after vaccination (seronegative individuals). Countries should consider introduction of the dengue vaccine CYD-TDV only if the minimization of risk among seronegative individuals can be assured [4].

For countries considering vaccination as part of their dengue control programme, pre-vaccination screening is the recommended strategy [5]. With this strategy, only persons with evidence of a past dengue infection would be vaccinated (based on an antibody test, or on a documented laboratory confirmed dengue infection in the past). If pre-vaccination screening is not feasible, vaccination without individual screening could be considered in areas with recent documentation of seroprevalence rates of at least 80% by age 9 years.

Screening tests would need to be highly specific to avoid vaccinating truly seronegative persons and to have high sensitivity to ensure that a high proportion of seropositive persons are vaccinated. Conventional serological testing for dengue virus IgG (e.g. dengue IgG enzyme-linked immunosorbent assay (ELISA)) is available in most dengue endemic countries, and could be used to identify persons who have had a past dengue infection. However, such laboratory-based assays do not provide results at the point of care. Point-of-care tests, i.e. rapid diagnostic tests (RDTs), would facilitate the implementation of the pre-vaccination screening strategy, but to date none have been validated or licensed specifically for the detection of past dengue infection. Use of currently available IgG-containing RDTs – despite their lower sensitivity for detection of past dengue infection compared with conventional dengue IgG ELISA – could be considered in high transmission settings until better RDTs for determining serostatus become available.

No screening test is likely to be 100% specific due to potential cross-reactivity with other flaviviruses. In settings with high dengue seroprevalence, a test with lower specificity might be acceptable as the proportion of seronegative individuals incorrectly vaccinated would be low. A pre-vaccination screening strategy may also be considered in low-to-moderate transmission settings. In settings with low seroprevalence a test with high specificity is

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needed. Given the limitations regarding specificity, some seronegative individuals may be vaccinated because of a false positive test result. Furthermore, as vaccine-induced protection against dengue in seropositive individuals is high but not complete, breakthrough disease will occur in some seropositive vaccinees. These limitations will need to be communicated to populations offered vaccination.

Decisions about implementing a pre-vaccination screening strategy with the currently available tests will require careful assessment at the country level, including consideration of the sensitivity and specificity of available tests and of local priorities, dengue epidemiology, country-specific dengue hospitalization rates, and affordability of both CYD-TDV and screening tests.

Decisions about implementing a seroprevalence criterion-based vaccination strategy without individual screening in areas with documented seroprevalence rates of at least 80% at age 9 years will require population serosurveys at high resolution, i.e. at district and sub-district level. Careful assessment is required with regard to the feasibility and cost of population seroprevalence studies. Communication needs to ensure appropriate and full disclosure of the risks of vaccination of persons with unknown serostatus.

Vaccination should be considered as part of an integrated dengue prevention and control strategy. There is an ongoing need to adhere to other disease preventive measures such as well-executed and sustained vector control. Individuals, whether vaccinated or not, should seek prompt medical care in if dengue-like symptoms occur. Vaccinated patients should continue to be offered the best evidence-based clinical care for all patients with dengue.

1. Selection of target age group for vaccination

Whether there are age-specific effects, independent of serostatus, is the subject of ongoing research. Currently, the vaccine should be used within the indicated age range, which in most countries is 9–45 years. The age group to target for vaccination depends on the dengue transmission intensity in a given country, and will be lower in countries with high transmission, and higher in countries with low transmission. The optimal age group to be targeted is the age before which severe dengue disease incidence is highest; this can be ascertained from national and subnational routine hospital laboratory-confirmed surveillance data.

2. Vaccination schedule

In the absence of longer-term data on vaccine efficacy and safety with fewer than 3 doses, CYD-TDV is recommended as a 3-dose series given 6 months apart. Should a vaccine dose be delayed for any reason, it is not necessary to restart the course and the next dose in the series should be administered as soon as possible.

There are currently no data on the use of booster doses. Additional studies to determine the utility of a booster dose and its best timing are in progress. At this time there is no recommendation concerning a booster dose.

3. Special settings and populations

Outbreak response. CYD-TDV should not be considered as a tool for outbreak response.

Pregnant women. CYD-TDV is not recommended in pregnant and lactating women because insufficient data are available on its use in pregnancy. However, the limited data generated from inadvertent vaccination of pregnant women that occurred during clinical trials have not identified a specific risk. If a woman becomes pregnant before all 3 doses have been administered, the remaining doses should be given after lactation has been concluded.

Immunocompromised persons. Due to lack of data, CYD-TDV is contraindicated in immunocompromised individuals.

Travellers. In travellers who have already had a documented dengue illness or are seropositive, vaccination before travel to high dengue transmission settings could be considered.

4. Surveillance

Dengue surveillance should be strengthened, particularly in the context of infections with clinical similarities to dengue (including emerging infections such a Zika virus infection). In areas of the world for which there is a paucity of data, further characterization of the burden of dengue, which appears to be growing, is needed. Use of standardized case definitions is encouraged to enhance data sharing and comparability across regions. With the potential increase in false-positive results from serological testing of CYD-TDV vaccinated individuals, diagnostic testing of an acute dengue infection should move to virological confirmation (such as polymerase chain reaction (PCR)) whenever possible. The use of surveillance data to monitor population impact of a vaccination programme may be challenging as the year-to-year variability in dengue transmission may be greater than the expected vaccine impact.

5. Research priorities

There is an urgent need for the development of highly specific and sensitive RDTs for determination of dengue serostatus. Research is also needed to evaluate vaccine schedules with fewer doses, and to assess the need for booster doses. Locally applicable cost-effectiveness studies are needed to support policy decisions. Research on how best to implement and integrate pre-vaccination screening in an immunization programme is recommended.

The development of safe, effective, and affordable dengue vaccines for use irrespective of serostatus remains a high priority.

References

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